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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,072	01/25/2002	Genoveffa Franchini	1662.018US1	1664

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/048,072	FRANCHINI, G., ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-10,12-17 and 20-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-10,12-17 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/07/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Serial No.: 10/048,072 **Docket No.:15280-4003US**
Applicants: Franchini, G., *et al*. **Filing Date: 01/25/02**

Detailed Office Action

Status of the Claims

Claims 1-3, 7-10, 12-17 and 20-22 are currently under examination.

37 C.F.R. § 1.98

The information disclosure statement filed 07 January, 2008, has been placed in the application file and the information referred to therein has been considered.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-3, 7-10, 12-17 and 20-22 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As previously set forth, the claims are directed toward methods of inducing HIV-1-specific $CD8^+$ immune responses in infected individuals by administering a recombinant virus

encoding HIV-1 structural proteins (e.g., Gag, Pol, or Env) or a non-structural protein (e.g., Nef). Additional claim stipulations require the composition to be administered to patients with viral loads <10,000 copies per ml of plasma and $CD4^+$ cell counts >500 cells/ml. The claims also encompass reductions in viral load by administering compounds that induce HIV-1-specific CTL responses.

As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide sufficient guidance pertaining to those HIV or retroviral immunogens that are capable of inducing therapeutic HIV-specific $CD8^+$ immune responses. The claims are broadly directed toward any recombinant viral vaccine encoding a peptides obtained from HIV or retroviral Gag, Pol, Env, or Nef proteins. The disclosure fails to provide sufficient guidance pertaining to the molecular determinants modulating therapeutic HIV-specific $CD8^+$ immune responses. Which HIV or retroviral

proteins/polypeptides contain protective CTL epitopes? Which viral constructs are capable of expressing the immunogens of interest for a sufficient period of time to induce an HIV-specific $CD8^+$ immune response of the proper specificity, titer, and duration? The claimed invention basically requires that the skilled artisan guess as to which constructs and immunogens will provide the desired immune response.

2) The disclosure fails to provide sufficient guidance pertaining to the correlates of human protection. Currently, the correlates of human protection remain to be elucidated. To date, it is not clear what type of immune response is required to provide a therapeutic benefit. As Pantaleo and Koup (2004) note (see left col., p. 808) "There is still no direct experimental evidence...that HIV-1-specific cellular immunity prevents disease progression." There appears to be some suggestion that both polyfunctional (IL-2 and IFN-γ) $CD4^+$ and viral-specific $CD8^+$ T-cell responses are involved. The disclosure fails to address either of these considerations. Moreover, $CD8^+$ T-cell responses by definition are not protective in nature. CTL vaccines do not prevent infection, but rather control the spread of virus. As McMichael and Hanke (2003) state (see left col., p. 876) "Whereas neutralizing antibodies can prevent infection, $CD8^+$ T-cell responses cannot. These cytotoxic T lymphocytes (CTLs) react to other cells of the body that are infected by HIV and present peptide fragments of viral proteins bound to MHC class I proteins." The authors further conclude that "A vaccine should stimulate high numbers of $CD8^+$ T memory cells, which rapidly release cytokines and chemokines on subsequent antigen contact and start killing target cells (Fig. 2). But these cells may need to be expanded to out-number the virus-infected cells and distributed to several sites around the body. Thus, full

antiviral activity may take days to develop and will only control, rather than prevent, viral infection." The specification is silent concerning these issues.

3) The disclosure fails to provide sufficient guidance pertaining to the *quasispecies* nature of HIV infection that ultimately leads to viral evasion and escape. The plasticity of the HIV-1 genome and its contribution to immune escape are salient factors that have prevented the development of an effective vaccine. HIV-1 exists as a large pool of genotypically and phenotypically distinct isolates. It has been well-documented that the virus relies upon this heterogeneity to escape immune surveillance and detection (McMichael and Hanke, 2003). For instance, the majority of the neutralizing antibody response is directed toward a molecular determinant (V3) that undergoes rapid mutation. Thus, even when a neutralizing antibody or $CD8^+$ response is generated, it rapidly becomes ineffective as other members of the *quasispecies* quickly replicate and grow out. The disclosure fails to provide any guidance concerning the identification of HIV or retroviral CTL epitopes that are resistant to viral escape.

4) The disclosure fails to provide any working embodiments. As noted *supra*, the claims encompass considerable breadth pertaining to the viral construct (i.e., source of viral expression vector, HIV/retroviral immunogens expressed). The only examples provided in the specification are purely prophetic and fail to provide any meaningful data. Some data was provided from a macaque model, however, this model is not an art-recognized model for vaccine development. Although animal models, such as the macaque system, are capable of providing important information pertaining to the understanding of pathogenesis and immunity, the results from such studies cannot be directly extrapolated to a clinical setting due to the structural differences between SIV and HIV (Haigwood,

2004). As Haigwood (2004) concludes (see abstract, p. 187) "By necessity, animal models can only be validated after successful trials in humans and the determination of correlates of protection. Because the only vaccine product tested in phase III trials in humans failed to achieve the desired protective threshold, we are as yet unable to validate any of the currently used nonhuman primate models for vaccine research." Pantaleo and Koup (2004) also concluded (see right col., p. 809) that "it is also unclear what data from which animal model of HIV-1 infection are most relevant to human infection and vaccine protection." Additional limitations pertaining to the macaque model were reviewed by Feinberg and Moore (2002) who note (see left col., p. 207) that "because HIV-1 does not productively infect macaques, it cannot be used as a challenge virus to assess whether a given vaccine can prevent or ameliorate infection[1,2]. Hence, preclinical AIDS vaccine models rarely test the identical vaccine constructs that are planned for human use. Instead, studies in rhesus macaques explore the potential protective efficacy of vaccine concepts, not the actual vaccines being developed for human trials."

5) The state-of-the-art vis-à-vis HIV CTL vaccine development can be characterized by unpredictability (Haynes *et al*., 1996; Burton and Moore, 1998; Moore and Burton, 1999; Desrosiers, 2004; Burton and Moore, 1998; Pantaleo and Koup, 2004; Haigwood, 2004; Altes *et al*., 2002; McMichael and Hanke, 2003; Feinberg and Moore, 2002; Stott and Almond, 1995). To date, there is not one single effective HIV CTL vaccine on the market. Several clinical trials have been conducted but in every situation, the immunogen failed to induce a long-lasting and high-titer immune response. Common problems encountered with vaccine development include the extraordinary variability, or *quasispecies* nature of HIV, the

lack of an exact animal model of HIV-induced AIDS, and the lack of understanding of the correlates of protective immunity. The disclosure fails to address these concerns. Moreover, applicants are reminded that enablement is determined as of the effective filing date of the application (28 July, 1999). *Chiron Corp*. v. *Genentech Inc*., 363 F.3d 1247, 1254, 70 U.S.P.Q.2d 1321, 1325-26 (Fed. Cir. 2004). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.2d 1123, 1128, 190 U.S.P.Q. 402,405-06 (C.C.P.A. 1976); *In re Budnick*, 537 F.2d 535, 538, 190 U.S.P.Q. 422, 424 (C.C.P.A. 1976).

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Response to Arguments

Applicants' response failed to proffer any new experimental evidence or data obtained from peer-reviewed publications that addresses the aforementioned caveats. Applicants' additional arguments have previously been addressed. It was previously argued that the claims are directed toward a defined set of immunogens (e.g., Gag, gp120, Nef, or Pol). Applicants are reminded that the claimed invention is directed toward HIV Gag, gp120, Nef, or Pol peptides. This term is not clearly defined in the specification but can reasonably be interpreted to mean anything from small CTL epitope-containing fragments to the full-length proteins. Contrary to applicants' assertion the

disclosure fails to provide a detailed analysis of suitable CTL epitopes, particularly those that will be therapeutic.

Applicants again argue that the claims are not directed toward protective immune responses *per se*, and so the issues associated with vaccine development are not germane. Perusal of the disclosure (page 1, lines 18-21) reveals that "This invention relates to an improved method of maintaining an immuno-protective response in persons infected with a retrovirus after highly active anti-retroviral therapy (HAART)." The specification further states (see page 2, lines 6-9) that "The method can use a vaccine that is a DNA based vaccine or that is an attenuated recombinant virus. A preferred virus is an attenuated poxvirus, particularly NYVAC and ALVAC, attenuated vaccinia and canarypox viruses respectively. Other attenuated pox viruses such as MVA can also be used." Thus, the claimed invention clearly encompasses therapeutic vaccine responses. Accordingly, the issues raised *supra* pertaining to CTL vaccine development are directly relevant.

It was again argued that representative working embodiments are provided in the specification and a declaration involving human clinical trials was previously submitted. As clearly set forth above, to date there are no effective animal models with which to assess HIV vaccine efficacy. Furthermore, Dr. Franchini indicated that preliminary results have been obtained from a clinical trial involving ACTG5054 which is an ALVAC recombinant encoding Gag, PR, and Env. Applicants noted that a reduction in viral load was observed in this study. Applicants are again reminded that the claims are not directed toward any particular expression vector or HIV/retroviral epitope. Considering the unpredictability of the prior art, a single

example would be insufficient to enable the full breadth of the claimed invention.

Accordingly the rejection is deemed to be proper and is hereby maintained. Applicants' representative is invited to contact the examiner to discuss these issues further.

Final Office Action

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Bruce R. Campell, Ph.D., can be reached at (571) 272-0974. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing

System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

/Jeffrey S. Parkin, Ph.D./
Primary Examiner, Art Unit 1648

30 March, 2008

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/048,072	FRANCHINI, G., ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	